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Increase of sentinel lymph node melanoma staging in The Netherlands; still room and need for further improvement

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Practice points

- Twenty-three years after the introduction of minimally invasive sentinel lymph node staging for melanoma, sentinel lymph node biopsy (SLNB) was performed in 65% of the eligible Dutch patients with melanoma in 2016.
- In The Netherlands, large regional differences persist in the performance of SLNB in stage IB–II melanoma, with 74% in the northeast compared with 56% in the rest of The Netherlands ($p < 0.01$).
- SLNB is less often performed in elderly patients and in those with head-and-neck melanoma.
- In The Netherlands, socioeconomic status no longer affected use of SLNB during the time period studied.
- Until promising noninvasive procedures and effective therapies emerge in the field of melanoma, further implementation of SLNB and adherence to melanoma guidelines, in accordance with the current eighth American Joint Committee on Cancer staging in melanoma, are indicated.

Aim: To investigate implementation of the seventh American Joint Committee on Cancer melanoma staging with sentinel lymph node biopsy (SLNB) and associations with socioeconomic status (SES). **Patients & methods:** Data from The Netherlands Cancer Registry on patient and tumor characteristics were analyzed for all stage IB–II melanoma cases diagnosed 2010–2016, along with SES data from The Netherlands Institute for Social Research. **Results:** The proportion of SLNB-staged patients increased from 40% to 65% ($p < 0.001$). Multivariate analysis showed that being female, elderly, or having head-and-neck disease reduced the likelihood of SLNB staging. **Conclusion:** SLNB staging increased by 25% during the study period but lagged among elderly patients and those with head-and-neck melanoma. In The Netherlands, SES no longer affects SLNB staging performance.

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Keywords: elderly • head and neck • melanoma • sentinel lymph node • socioeconomic status • staging

Sentinel lymph node biopsy (SLNB) in patients with American Joint Committee on Cancer (AJCC) stage IB–II melanoma was introduced in The Netherlands in 1996. The Dutch Society of Surgical Oncology and several regional working groups of The Netherlands Comprehensive Cancer Organization disseminated the SLNB staging model in The Netherlands.

Prospective studies, such as the Multicenter Selective Lymphadenectomy Trial (MSLT)-I and the more recent MSLT-II, demonstrated the staging and prognostic value of SLNB for stage IB–II melanoma [1–4]. Most patients are pleased with the outcomes of this minimally invasive staging procedure that yields good information with limited negative effects on quality of life [5,6]. MSLT-I results showed that SLNB is a low-morbidity procedure for staging the regional nodal basin in early melanoma and that complete lymph node dissection (CLND) is associated with lower morbidity compared with therapeutic lymph node dissection [2–4,7]. MSLT-II indicated an association of CLND with increased regional disease control. However, this benefit did not involve increased melanoma-specific survival compared with patients managed with positive SLNB and regular ultrasonography of the lymph node basin, with therapeutic lymph node dissection in case of regional recurrence [4].

Interferon (IFN) has been extensively studied in different regimens (high, intermediate, low dose, pegylated IFN, with or without induction phase, shorter and longer maintenance dose) in 15 adjuvant trials for advanced melanoma, but with a minimal effect overall [8]. The prognosis of stage III and IV melanoma has improved considerably in the last 10–15 years through targeted therapy with BRAF inhibitors (dabrafenib and vemurafenib) in BRAF-mutated disease, or with MEK inhibitors (trametinib and cobimetinib) and immunotherapy with the immune checkpoint inhibitors anti CTLA-4 antibody (ipilimumab) and anti-PD1 antibodies (nivolumab and pembrolizumab) [9]. In addition to these new, effective systemic therapies, two new intralesional therapies are in current trials. One is intralesional local melanoma treatment with talimogene laherparepvec, an oncolytic virus therapy. The other involves chemoablation with intralesional Rose Bengal, a small-molecule oncolytic immunotherapy [10,11]. Either of them, used for the treatment of in-transit metastases or metastatic disease, may also enhance the patient immune system. Targeted and/or immunotherapy treatment may improve disease-free and overall survival for patients with stage III and IV melanoma. Optimal staging of clinical stage IB–II melanoma is therefore indicated to identify patients with high-risk stage IIIA disease who might also benefit from these new therapies.

Seventeen years after the introduction of SLNB staging for melanoma, this procedure was performed in less than 50% of all eligible patients in The Netherlands. Considerable practice variation has been observed in SLNB procedures among the eight cancer regions of the Comprehensive Cancer Organization, ranging from 22.5 to 56.5% [12,13]. The revised Dutch melanoma guideline of 2012 advised SLNB staging for stage IB–II melanoma. However, in 2014, only 25% of melanoma-treating specialists in The Netherlands endorsed the need for SLNB for regional staging of stage IB–II disease. Residents endorsed at a higher rate, but still at only 44% [14]. Furthermore, in patients with head-and-neck melanoma, older patients and patients with a low socioeconomic status (SES), SLNB was less frequently performed. It was used more often in patients with T3 melanomas and those diagnosed with melanoma in a university hospital [12,13,15].

The aim of the current study was to update information about the performance of SLNB in The Netherlands in clinical stage IB–II melanoma after implementation of the seventh edition of the AJCC staging manual in 2010 [16], which included sentinel lymph node staging. This aim was selected because high-risk patients might benefit from new systemic therapies and to allow comparison of these results with previous reports from The Netherlands among cancer regions and provinces and investigation of the role of SES in SLNB implementation.

Methods

Study population

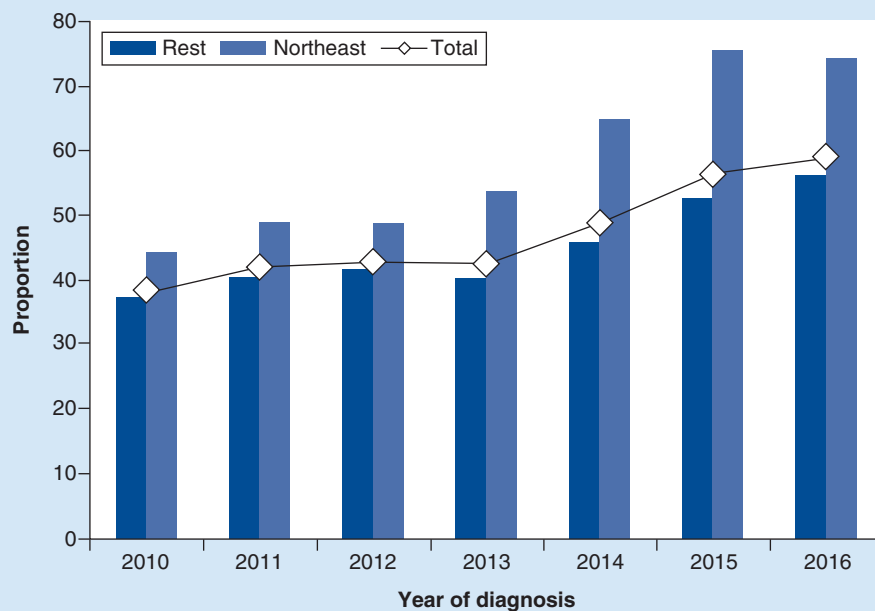
This study included all patients with localized melanoma stage IB–II diagnosed 2010–2016. Data were retrieved from The Netherlands Cancer Registry, embedded within The Netherlands Comprehensive Cancer Organization [17]. This population-based registry relies on notification by the automated nationwide network and registry of histopathology and cytopathology in The Netherlands and is complemented by other sources such as a national registry of hospital discharge and radiotherapy institutes. Data collection was conducted according to the declaration of Helsinki ethical principles for medical research involving human subjects [18].

After notification, fully trained registrars routinely collected data from pathology reports and patient files in all Dutch hospitals. Data were collected on patient and tumor characteristics, such as age, sex, tumor localization of the primary melanoma and tumor stage. Information about the performance and outcome of SLNB was retrieved from the medical records. Patients with clinically suspicious or palpable lymph nodes, distant metastases and/or a history of lymph node dissection were excluded. SES scores were assigned to different postal code areas by The Netherlands Institute for Social Research and calculated based on income, employment and level of education [19]. Calculated scores give an estimate of the SES in the particular postal code area where a patient resides. Calculated SES scores are divided into five groups: SES = 1 (low) to SES = 5 (high).

To render the data from this study comparable to those from previous studies with respect to the SLNB staging in The Netherlands, the northeastern part of the country was compared with the rest of The Netherlands, as were the eight cancer regions and provinces [12,13]. This approach made it possible to investigate the role of the Dutch Society of Surgical Oncology and several regional working groups of The Netherlands Comprehensive Cancer Organization in the dissemination of the SLNB approach.

Statistical analysis

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., NC, USA). Patient characteristics were compared between the northeastern provinces and the rest of The Netherlands using Chi-square or Mann–



Number of patients by region

Rest	1747	1822	1978	2505	2504	2470	2644
Northeast	376	450	474	552	510	517	551
Total	2123	2272	2452	3057	3014	2987	3195

Figure 1. Trend in the proportion of sentinel lymph node biopsy performed per year of diagnosis in all patients with stage IB–II melanoma in The Netherlands; comparison among topographical regions.

Whitney U tests (the latter with nonnormally distributed data). Also, patient characteristics from SLNB-positive and -negative cases were compared. Multivariable logistic regression analysis was performed to estimate the odds for undergoing SLNB. Values were adjusted for factors that could influence the decision to perform SLNB (e.g., region, age, primary lesion location, Breslow thickness, pathological stage of primary tumor, SES). $p < 0.05$ was considered statistically significant.

Results

During the study, a total of 19,100 patients with stage IB–II melanoma were registered (9344 males (49%) and 9756 females (51%)). SLNB was performed in 9163 (48%) overall. The proportion of melanoma patients who received SLNB increased, however, from 40% in 2010 to 65% in 2016 (Figure 1). The procedure was performed significantly more often in the northeastern part of The Netherlands compared with the rest of the country ($p < 0.01$; Table 1 & Figure 1). An overview of the percentage SLNBs performed in each province in The Netherlands is presented in Figure 2.

Of the 9163 patients who underwent SLNB, positive nodes were found in 1877 patients (20%; Table 2). No differences were found in patient or tumor characteristics and sentinel node positivity between the northeastern part of The Netherlands and the rest of the country (data not shown).

Median age at diagnosis in the SLNB group was 58 (interquartile range [IQR], 47–68) years, compared with 67 (IQR: 53–78) years in the group that did not undergo SLNB ($p < 0.001$). Tumors in the SLNB group were thicker (median Breslow thickness, 1.7 [1.2–2.8] mm, compared with 1.3 [0.9–2.7] mm in the non-SLNB group [$p < 0.01$]), and tumor stage at diagnosis was significantly higher ($p < 0.01$). Most primary melanomas were located on the trunk (37%), followed by the lower limb (27%), upper limb (21%), and head-and-neck region (15%). Significantly fewer SLNBs were performed among patients with melanomas located in the head-and-neck area ($p < 0.01$; Table 1). Figure 2 presents an overview by province of the percentage of SLNBs performed in

Table 1. Characteristics of all patients with stage IB–II melanoma in The Netherlands, diagnosed 2010–2016, comparison between groups (sentinel lymph node biopsy [yes/no]).

		SLNB performed		No SLNB performed		Total		p-value
		n	%	n	%	n	%	
Gender								0.3 [¶]
– Male		4518	49	4826	49	9344	49	
– Female		4645	51	5111	51	9756	51	
Age (years) at diagnosis								<0.01 [¶]
– 15–29		392	4	229	2	621	3	
– 30–44		1489	16	1001	10	2490	13	
– 45–59		3120	34	2258	23	5378	28	
– 60–74		3278	36	3254	33	6532	34	
– >75		884	10	3195	32	4079	21	
Median age (years) (Q1–Q3)	58	(47–68)	67	(53–78)	62	(49–73)		<0.01 [#]
Location primary								<0.01 [¶]
– Head/neck		590	6	2269	23	2859	15	
– Trunk		3737	41	3296	33	7033	37	
– Arm		2017	22	2048	21	4065	21	
– Leg		2814	31	2308	23	5122	27	
– Overlapping		5	0	16	0	21	0	
Breslow thickness (mm)								<0.01 [¶]
– <1		1155	13	3307	33	4462	23	
– 1–2		4352	47	2983	30	7335	38	
– 2–3		1710	19	1136	11	2846	15	
– 3–4		808	9	635	6	1443	8	
– >4		1020	11	1421	14	2441	13	
– Unknown		118	1	455	5	573	3	
Median Breslow thickness (Q1–Q3)	1.7	(1.2–2.8)	1.3	(0.9–2.7)	1.5	(1.1–2.75)		<0.01 [#]
pT								<0.01 [¶]
– 1B		1132	12	3254	33	4386	23	
– 2		4503	49	3099	31	7602	40	
– 3		2539	28	1764	18	4303	23	
– 4		952	10	1372	14	2324	12	
– X		37	0	448	5	485	3	
SES								0.2 [¶]
– 1	(low)	1560	17	1712	17	3272	17	
– 2		1729	19	1843	19	3572	19	
– 3		1877	20	2100	21	3977	21	
– 4		1876	20	2109	21	3985	21	
– 5	(high)	2121	23	2173	22	4294	22	
Region [†]								<0.01 [¶]
– Northeastern	part [‡]	2044	22	1386	14	3430	18	
– Rest	§	7119	78	8551	86	15,670	82	
– Total		9163	48	9937	52	19,100	100	

Data are displayed as n (%) or median (interquartile range).

[†]Topographic region in The Netherlands.[‡]Northeastern part (Groningen, Friesland, Drenthe and Overijssel).[§]Rest of the provinces in The Netherlands.[¶] χ^2 -test.[#]Mann–Whitney U test, significant p-values in bold (p < 0.05).

pT: Pathological primary tumor stage; Q1–Q3: Interquartile range; SES: Social economic status; SLNB: Sentinel lymph node biopsy.

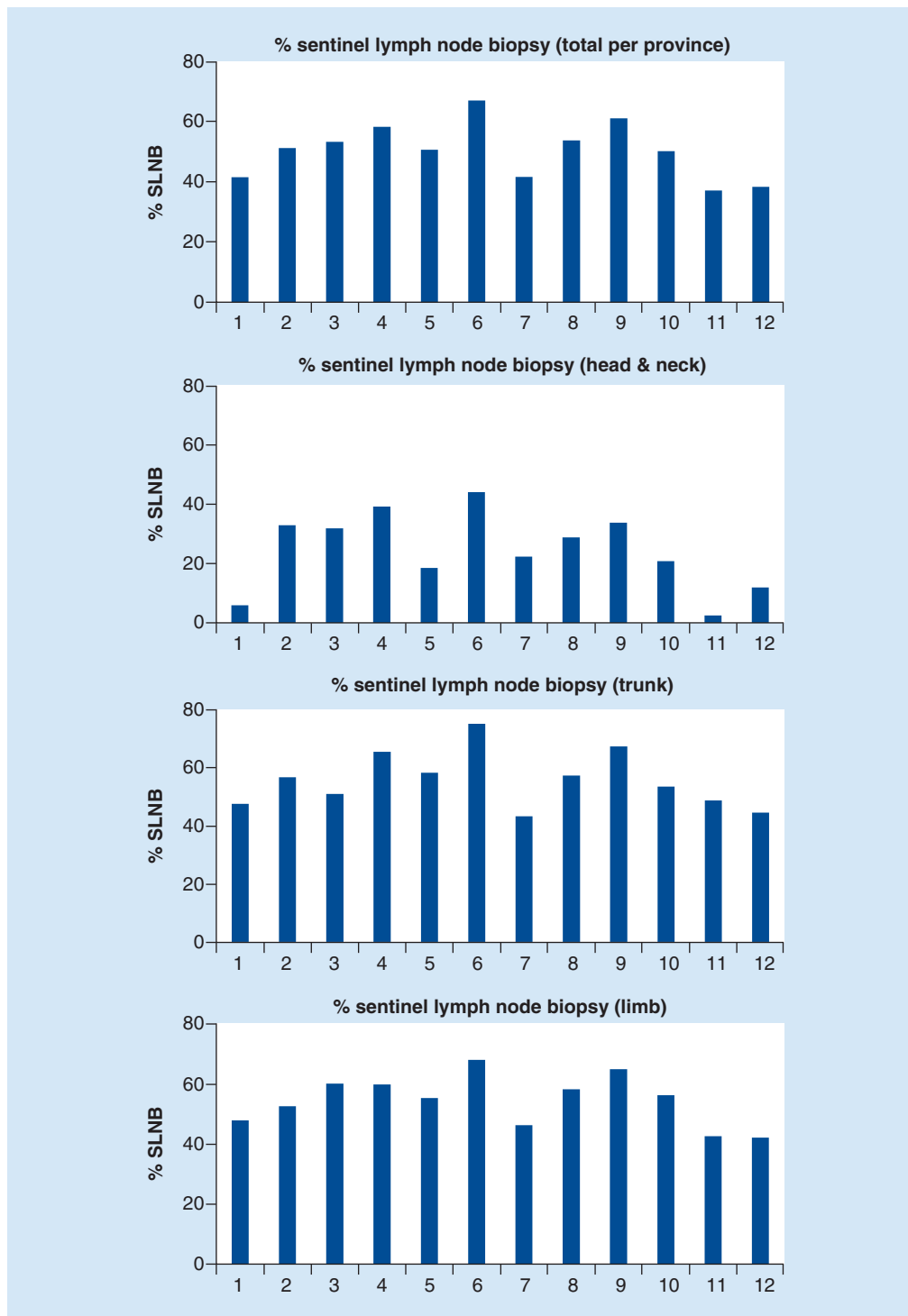


Figure 2. Percentages of sentinel lymph node biopsies per province in The Netherlands; comparison among different anatomical locations of the primary melanoma.

melanomas located in the head-and-neck region, trunk and limbs. No significant differences in SES were found between the SLNB and non-SLNB groups ($p < 0.2$; Table 1).

After adjustment for sex, age, tumor location, Breslow thickness, SES and tumor stage, multivariate analysis showed that SLNBs were more often performed in the northeastern part of The Netherlands (odds ratio [OR],

Table 2. Sentinel lymph node biopsy positivity in Dutch patients with melanoma between 2010 and 2016, by topographical region in The Netherlands (n = 9163).

	Northeastern part [†]		Rest [‡]		Total		p-value
	n	%	n	%	n	%	
SLNB							p = 0.7 [§]
Negative	1595	78	5598	79	7193	79	
Positive	425	21	1452	20	1877	20	
Not found/unknown	24	1	69	1	93	1	
	2044	22	7119	78	9163	100	

Data are displayed as n (%).
[†]Northeastern part (Groningen, Friesland, Drenthe and Overijssel).
[‡]Rest of the provinces in The Netherlands.
[§]χ²-test, significant p-values in bold (p < 0.05).
SLNB: Sentinel lymph node biopsy.

2.2; 95% confidence interval, 2.01–2.41; Table 3). Females were less likely to undergo SLNB (OR: 0.9; 95% CI: 0.84–0.96; p < 0.05), and SLNB rates decreased with increasing age. Patients with head-and-neck melanomas underwent SLNBs less often (head/neck vs limb: OR: 0.24; 95% CI: 0.21–0.27; p < 0.05). SLNB was performed slightly more often among patients from a high SES class (score > 5) when compared with low SES (OR, 1.2; 95% CI: 1.04–1.29; p < 0.05; Table 3).

Discussion

This study showed that in 2016, a quarter of a century after its introduction, SLNB was performed in only 65% of eligible Dutch patients with melanoma. In females, elderly patients and those with head-and-neck melanoma, the staging procedure was performed even less frequently. However, SES no longer significantly affected the likelihood of SLNB staging, a change from the association before 2010 [12].

The fourth revision of the Dutch melanoma guidelines published in 2004 advised using SLNB in patients with stage IB or higher melanoma who wanted to be optimally informed about their prognosis. The SLNB staging procedure was therefore not part of the standard workup of patients with clinical stage IA-II melanoma. Since 2004, the percentage of SLNBs performed in cases of melanoma increased in The Netherlands from 24% to 55% in 2011 [12,13].

The 5th revision of the Dutch melanoma guideline in 2012, based on the seventh edition of the AJCC staging manual that went into effect in 2010 [16], advised SLNB for stage IB–II melanoma and discussed the potential benefits and drawbacks of CLND in case of sentinel node positivity. Recently, effective adjuvant targeted and immune systemic therapies for stage III melanoma have become available. Therefore, adequate staging is even more important, emphasizing the need for insight into the current application of SLNB in The Netherlands.

Large regional differences persist in the use of SLNB in stage IB–II melanoma. Melanoma guidelines are more often met in academic centers [20]. In the Northeast, the percentage was in 74% in 2016, compared with 56% in the rest of The Netherlands (p < 0.01). These results are promising and in keeping with the trend in the northeast, but higher percentages of SLNB performance should be feasible. The current 65% rate of SLNBs is comparable to previously reported percentages in the USA, from 47% to 60% [21–24]. However, the percentage of SLNB performed in melanoma remains lower than the almost 80% rate in breast cancer [25]. An explanation might be that in melanoma, physicians who perform the diagnostic excision and re-excision (if indicated) lack the surgical skills or opportunity to perform SLNB. Another reason might be that physicians found no indication for SLNB based on MSLT-II results, because it is only a diagnostic procedure and no longer a therapeutic intervention.

SLNB also can be applied without a good basis. A recent Dutch study showed that use of SLNB in noneligible melanomas according to the Dutch melanoma guidelines was 2.9% [26]. In Germany, the percentage of SLNB staging for melanoma is 88% [27,28]. An explanation for the high percentage might be that German dermatologists are ‘melanomologists’ who manage the whole melanoma surgical and systemic treatment in-house [29]. In contrast, in The Netherlands and the USA, the melanoma health care landscape is more fragmented, divided among surgeons, dermatologists, plastic surgeons, head-and-neck surgeons, medical oncologists and in The Netherlands, even per province and cancer region. This mosaic of care might explain the great variation in SLNB uptake not only in The Netherlands but also in countries like the USA.

Table 3. The likelihood of performing sentinel lymph node biopsy adjusted for multiple variables in Dutch patients with melanoma: a multivariate analysis.

		OR	95% CI	
Region				
– Northern	Part [†]	2.20	2.01	2.41
– Rest	‡	Ref.		
Gender				
– Male	Ref.			
– Female		0.90	0.84	0.96
Age (years) at diagnosis				
– 15–29	Ref.			
– 30–44		0.79	0.64	0.97
– 45–59		0.67	0.55	0.82
– 60–74		0.45	0.37	0.54
– >75		0.11	0.09	0.13
Location primary				
– Head/neck		0.24	0.21	0.27
– Trunk		0.90	0.80	1.03
– Limb	§	Ref.		
– Overlapping		0.26	0.09	0.70
Breslow thickness (mm)				
– <1	Ref.			
– 1–2		2.20	1.70	2.90
– 2–3		2.30	1.60	3.30
– 3–4		2.10	1.50	3.10
– >4		2.00	1.40	2.80
– Onbekend		2.60	1.80	3.90
pT				
– 1B	Ref.			
– 2		2.60	2.00	3.30
– 3		3.60	2.50	5.10
– 4		2.20	1.60	3.20
– x		0.20	0.12	0.33
SES				
– 1	Low	Ref.		
– 2		1.02	0.91	1.14
– 3		1.06	0.95	1.18
– 4		1.05	0.94	1.17
– 5	High	1.17	1.04	1.29
Data are displayed as odds ratio with 95% CI.				
†Northeastern part (Groningen, Friesland, Drenthe and Overijssel).				
‡Rest of the provinces in The Netherlands,				
§Limb (lower and upper extremity).				
Significant odds ratios in bold (p < 0.05).				
OR: Odds ration; pT: Pathological tumor stage; Ref.: Reference; SES: Socioeconomic status.				

Age and melanoma located in the head-and-neck region remain important predictors of whether to perform SLNB. As in this study, an investigation in the general US population found noncompliance with National Comprehensive Cancer Network melanoma guidelines on SLNB for elderly patients and for melanoma located in the head and neck [20,24,30]. With melanoma, as for breast cancer, comorbidity could be a limiting factor in whether or not to perform SLNB. It is also possible that elderly patients, their family, caregivers and treating physicians decide on a more conservative treatment approach balanced against an existing shorter life expectancy.

Performance of SLNB in women was less likely in The Netherlands, although median Breslow thickness was 1.40 (IQR: 1.0–2.5) mm in women compared with 1.70 (IQR: 1.1–3.0) mm in men. This finding of lower rates of SLNB in women is remarkable because it was adjusted for other factors (e.g., age, primary lesion location, pathological stage of the primary tumor, Breslow thickness, SES) that could influence the decision to perform SLNB. Recently, El Sharouni *et al.* hypothesized two explanations for the differences in sex-specific decision-making: medical information may be perceived differently, or there may be a clinician-specific sex bias when approaching and informing female patients [26].

The SLNB positivity rate in this study was 20%, which is comparable to other studies showing between 15 and 22% [28,31,32], as was the location of the primary melanoma [28]. We found that SLNB was performed in 21% of eligible patients with head-and-neck melanoma in The Netherlands, compared with 17% in a study that included data up to 2014 [26]. Noncompliance with SLNB recommendations was also found in the U.S. general population for head-and-neck primary lesions (OR: 2.0; 95% CI, 1.9–2.2) [20,24]. SLNB procedures in the head-and-neck area are technically difficult, even for experienced surgeons, because of the small incisions, critical anatomical structures and great variation in atypical and/or multiple drainage sites [33–36]. SLNBs and re-excision procedures of limb and trunk melanoma can be safely performed under local anesthesia [37]. In contrast, SLNBs for melanoma located in the head-and-neck region often require general anesthesia that might introduce additional morbidity. These two reasons might explain the low rates of SLNB performed in patients with head-and-neck melanoma.

In contrast to a previous study performed in The Netherlands, our findings demonstrate that SES no longer affected SLNB rates during the time period studied [15]. Although SLNB was performed slightly more often among patients with high SES, it is now routinely performed in The Netherlands for patients with lower SES, as is the case in Germany, where Livingstone *et al.* also found no SES influence on SLNB rates [28].

SLNB for melanoma is a minimally invasive staging procedure, accompanied by minimal treatment-related short- and long-term morbidity [5,7,38–41]. Negative SLNB had no negative effects on quality of life [6]. The quality of life in Dutch melanoma survivors after axillary or inguinal SLNB, with or without CLND, is even better than that in a norm group [5]. This suggests that performing SLNB in melanoma patients is a minimal invasive procedure beneficial for the patients without affecting quality of life.

Compliance with national melanoma guidelines and using an integrated multidisciplinary approach through case discussions in the melanoma tumor board will improve melanoma-specific, disease-free and overall survival. In addition, there must be room for shared decision making among treating patients, physicians and caregivers, with specific assessments of each patient's ultimate goals of care.

The new, successful treatment of advanced melanoma with targeted and immunotherapies has changed overall melanoma care in The Netherlands. Each case of advanced melanoma today is discussed at one of 13 melanoma centers in The Netherlands with respect to (combined) treatment. The promising results achieved with the targeted and immunotherapies have meanwhile led to increased consultations between hospitals and melanoma centers with regard to treatment of patients with sentinel node-positive melanoma. The expectation is that further implementation of SLNB staging will now rapidly take place in The Netherlands.

Limitations

There are several limitations with this study. The reason for offering the patient SLNB or not as a minimally invasive staging procedure of the regional nodal basin was unknown. Surgeons, plastic surgeons, head-and-neck surgeons and dermatologists likely differed in reasons for staging a localized melanoma with SLNB, and the patient's reasons for accepting or declining a SLNB were not recorded. Also unknown was whether the cases were discussed in a melanoma tumor board or if there was a consultation with the regional melanoma tumor board of one of the eight comprehensive cancer centers. Because of general data protection regulations in The Netherlands, the Comprehensive Cancer Center was unable to retrieve some percentage of SLNBs performed at the various hospitals, and instead data respective to the provinces were provided.

Conclusion

Twenty-three years after the introduction of minimally invasive sentinel lymph node staging for melanoma, SLNB was performed in 65% of the eligible Dutch melanoma patients in 2016, although less often in elderly patients, females and those with head-and-neck melanoma. Age and tumor location in the head-and-neck region might no longer be exclusion criteria, leaving only severe comorbidity or short life expectancy as contraindications. In The Netherlands, SES has ceased to be associated with the use of SLNB staging. Until promising noninvasive

procedures emerge in the field of melanoma staging, further implementation of SLNB and adherence to melanoma guidelines, in accordance with the current eighth AJCC staging in melanoma, are indicated, especially in view of the increasingly available effective drug targeted and/or immunotherapy for high-risk melanoma.

Future perspective

In addition to the importance of adequate staging in an era of novel therapies, other advantages should also be considered. First of all, follow-up after a negative SLNB can be reduced, along with the costs of melanoma follow-up in 39% of patients, without affecting quality of life [41,42]. Second, a personalized approach will be possible for sentinel lymph node-positive patients, using a wait-and-see policy and less frequent CLND [9,43,44].

In the optimization of sentinel lymph node staging in a noninvasive manner, ultrasonography is not an effective substitute for SLNB [45]. However, a promising technology of targeted fluorescence imaging in clinical stage IA-II melanoma is currently being explored using multispectral optoacoustic tomography (MSOT) (unpublished data). MSOT provides both anatomical and biological information and has the potential to identify sentinel lymph node metastatic involvement in patients with melanoma. Thus, when surgery is indicated, removal of only 'positive' sentinel lymph node(s) for further pathology examination and mutation analysis is possible.

Two recent studies, DeCOG and MSLT-II, showed that overall survival after a positive SLNB and CLND was not different from a delayed therapeutic lymph node dissection in case of a regional recurrence [4,46]. Will both of these negative studies now lead to less frequent offering of SLNB for stage IB–II melanoma according to the current eighth edition of the AJCC staging? Is SLNB, a minimally invasive staging procedure that provides optimal staging information with no clear survival benefit, still indicated? With the advent of effective systemic treatments for melanoma, including targeted or immunotherapies, optimal staging of stage IB–II melanoma appears to be a *sine qua non*. In the case of a positive SLNB, a melanoma tumor board should discuss further treatment decisions based on information about the number of positive SLNBs, nodal basin site and SLNB tumor burden (measured by maximum diameter of the largest focus or percentage area of the node). Further studies have to be performed to see if adjuvant systemic treatment for stage IIIA melanoma will improve disease-free and/or overall survival.

Author contributions

Study concepts: Deckers, Hoekstra, Louwman; study design: Deckers, Hoekstra, Louwman; data acquisition: Louwman; quality control of data and algorithms: Deckers, Hoekstra, Louwman; data analysis and interpretation: Deckers, Hoekstra, Louwman, Kruijff; statistical analysis: Louwman; manuscript preparation: Deckers, Hoekstra, Louwman, Kruijff; manuscript editing: Deckers, Hoekstra, Louwman, Kruijff and San Francisco Editing; manuscript review: Deckers, Hoekstra, Louwman, Kruijff.

Data sharing

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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